REMARKS

Claims 1, 4-10 and 14 are pending. A copy of the pending claims is attached for the Examiner's convenience. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

Rejections under 35 U.S.C. § 103

Claims 1, 4-10 and 14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Francis (U.S. Pat. No. 4,797,388, "Francis") in view of Levin et al. (Cancer Chemother. Pharmacol. 8:125-31 (1982), "Levin"). Applicant respectfully traverses.

To establish a *prima facie* case of obviousness under 35 U.S.C.§103, the Examiner must demonstrate a suggestion or motivation in the prior art to modify or combine the teachings of the references to arrive at the claimed invention. Further, the prior art must provide one of ordinary skill with a reasonable expectation of success.

Applicant respectfully submits that the present invention is not obvious over the cited references, Francis and Levin. The Examiner states that Francis is relied on to teach the broad aspect of the invention. Applicant respectfully disagrees and asserts that Francis does not teach the broad aspect of the present invention. The claims of the present invention are directed to methods of treatment of a host with a cellular proliferative disease. The methods comprise contacting the host with a composition consisting essentially of a pharmaceutically acceptable dianhydrogalactitol or analog and a pharmaceutically acceptable antiproliferative agent. The dianhydrogalactitol or analog and antiproliferative agent each are provided in an amount sufficient to modulate the cellular proliferative disease. The antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes. Conversely, Francis teaches use of galactitol to stabilize a

pharmaceutical compound prior to administration to a patient. The stability of therapeutic agents in the presence of galactitol is analyzed by incubating the agent/galactitol composition at 37^0C for one week. The ability of the composition to act as an anti-proliferative agent is never addressed. The composition taught by Francis finds use in stabilizing a pharmaceutical compound, not in treatment of an antiproliferative disease. Nothing in Francis indicates that the galactitol may serve a function as an active ingredient.

The Examiner further states that it would be obvious to look to Levin's teachings of combined therapy and the anti-tumor activity of hexitol epoxides and recognize that Francis' galactitol will function as an anti-tumor agent. However, as discussed in Applicant's previous response, there is no motivation to combine the cited references. "Obviousness cannot be established by combining the teachings of prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *In re Fritch* , 972 F.2d 1260, 1266; 23 USPQ2d 1780, (Fed. Cir. 1992). Applicant again asserts that one of skill in the art would not be motivated look to an article of Francis' nature to combine with Levin in order to arrive at the present invention. Levin addresses pharmacological benefits of various compounds; Francis addresses formulation of a therapeutic compound to increase its shelf-life. The Examiner cites *In re Heck* for the proposition that the use of patents as references is not limited to what the patentees describe as their own inventions or problems. Applicant respectfully points out that the holding in *In re Heck* was that a reference was properly included in an obviousness rejection because it was within the realm of the very narrow field of which the invention was concerned – that of cam-designing art. The reference was "directly related to the automotive camshafts with which Heck's invention is concerned" and "[p]ersons of ordinary skill in the cam-designing art are presumed to be familiar with this precise background." [*In re Heck,* 1040] In contrast, Francis and Levin are not part of the same narrow field of art. Francis is directed toward formulation of a pharmaceutical compound while Levin is concerned with treatment of a medical condition. One cannot say that these two areas of concern are both encompassed in a "very narrow field" or that one of skill in the art of formulating compounds would be expected to be

familiar with the use of compounds to treat anti-proliferative diseases, and vice versa. One of skill in the art looking to find additional agents to combine with dianhydrogalactitol to create a new anti-proliferative drug would not look to Francis as a source of potential compounds.

Furthermore, Applicant respectfully submits that even if Levin and Francis were combined, they would not have provided one of skill in the art with a reasonable expectation of success in practicing the present invention. Francis' disclosure regarding use of galactitol as a carrier for certain therapeutic agents would not provide any expectation of success that the combination of dianhydrogalactitol with an antiproliferative agent selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes, would result in a treatment more effective than that using dianhydrogalactitol or the anti-proliferative agent alone. Francis only relates to galactitol's ability to enhance the chemical and physical stability of a drug and to enhance reconstitution of the drug in water. Levin teaches that a combination of the compounds dianhydrogalactitol and BCNU is more successful in treating brain neoplasm than either compound alone. Levin further states that antitumor activities of hexitol epoxides may be enhanced by combination with other drugs. However, Levin also teaches that "DAG [dianhydrogalactitol] may have a limited place in central nervous system chemotherapy for specific types of tumors." Given the brief and ambivalent nature of Levin's disclosure and its lack of disclosure regarding the specific types of antiproliferative agents as set forth in the claims, one of skill in the art would not have an expectation that combining DAG with other anti-proliferative agents would result in a compound that is more effective in treating an anti-proliferative disease than the DAG and the anti-proliferative agent alone. Applicant respectfully reminds the Examiner that a rejection based on an "obvious to try" criterion is not proper under 35 U.S.C. § 103. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See also *The Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990). "An 'obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure,

but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *The Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1928 (CAFC 1990).

There is no teaching or motivation provided by these references to substitute the alkylating agent of Levin with an antiproliferative agent selected from the group of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes, each of which are not alkylating agents. Levin simply does not provide one of skill in the art with a reasonable expectation of success that combining dianhydrogalactitol or analog thereof with one of the antiproliferative agents recited in claim 1 would result in a successful combination therapy for treatment of proliferative diseases.

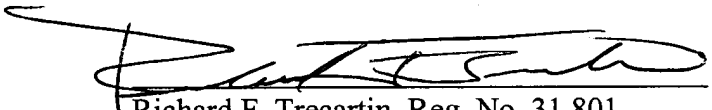
CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Applicants respectfully request that the Examiner call the undersigned attorney.

Respectfully submitted,

DORSEY & WHITNEY LLP

Date: October 20, 2003



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APPENDIX - PENDING CLAIMS

1. (previously presented) A method of treatment of a host with a cellular proliferative disease, comprising contacting said host with a composition consisting essentially of a pharmaceutically acceptable dianhydrogalactitol or analog thereof, and a pharmaceutically acceptable antiproliferative agent, each in an amount sufficient to modulate said cellular proliferative disease, wherein said antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes.

2-3. (canceled)

4. (previously presented) The method according to claim 1 wherein said antiproliferative agent is an intercalating agent.

5. (previously presented) The method according to claim 1 wherein said antiproliferative agent is a metal coordination complex.

6. (previously presented) The method according to claim 1 wherein said antiproliferative agent is cisplatin.

7. (previously presented) A method according to claim 1 wherein said dianhydrogalactitol or analog thereof is administered before the administration of said antiproliferative agent.

8. (previously presented) A method according to claim 1 when said dianhydrogalactitol or analog thereof is administered during the administration of said antiproliferative agent.

9. (previously presented) A method according to claim 1 wherein said dianhydrogalactitol or analog thereof is administered after the administration of said antiproliferative agent.

10. (original) The method of claim 1 wherein the modulation of said disease with said composition is greater than that for said antiproliferative agent alone.

11-13. (canceled)

14. (previously presented) A method according to claim 1 wherein said cellular proliferative disease is a solid tumor.